REMARKS / ARGUMENTS

1. No New Matter Has Been Added

No new matter has been introduced by way of this amendment. For each amendment made, proper support exists in the originally filed specification at the pages indicated.

2. Summary of Amendments

Claim 101 has been amended to indicate that the fibre "consists of" a coated end, and the words "at least partially" have been removed. Further, it is now clear that the fibre holding region is attached to the end of the fibre that is opposite to the coated end.

Claim 102 has been amended to specify that the coated end is further coated with the biocompatible protection layer, and the words "at least partially" have been removed.

Claim 105 has been amended to specify that the extraction phase is loaded with a calibrant prior to sampling.

3. Support for Claim Amendments Within Specification

In the interview with the Examiner on July 31, 2007, the Examiner recommended the above-noted amendments be made.

3.1. Amendments to Claim 101

Support for the amendment to claim 101, that the fibre consists of a coated end was made to distinguish over prior art having a coating that extends to the remainder of the fibre. This amendment clarifies that it is only the end of the fibre that is coated. Support can be found in the description and drawings.

In Figure 1, part A, reference numeral 4 (extraction phase) is depicted at the terminal end of reference numeral 2 (fibre or wire). The description of this figure states (page 16, lines 16 - 18):

> Figure 1, part A illustrates an extraction device 1 consists essentially of an extraction phase 4 coated on a fibre or wire 2 to be used with a positioning device to accurately locate the device in a tissue.

Other depictions of the coated fibre or wire, such as Figures 6 and 7, show the terminal end of the fiber (or wire) as coated with the extraction phase. There is no depiction or description of a fibre or wire in which more than the end is coated.

Claim 101 has been amended to indicate that the fibre holding region is attached to the end of the fibre that is opposite to the coated end. This is clearly depicted in Figure 1, part A, for example, in which the "handle" (8) is shown as the fibre holding region, and is located at the end of the fibre or wire (2) opposite to the extraction phase (4). In subsequent depictions (Figures 5, 6, and 7 for example), this same fibre holding region or "handle" is not labeled, but is clearly present, and is capable of moving the fibre into or out of a blood vessel, by rendering the fibre movable.

With reference to Figure 1, parts A (fibre with coated end and holding region or "handle", and B (catheter) it is clear that, upon assembly of the fibre into the catheter the fibre holding region could be used to pull up or push down on the fibre to cause movement with respect to the catheter, thereby moving the coated end of the fibre into or out of the blood vessel.

From page 16 (line 20) to page 17 (line 5), a description of the fibre, including a handle or fibre holding region, and a counterpart catheter is provided:

> The uncoated end of the wire may or may not include a handle 8 to facilitate positioning of the device. The length of the wire is variable 7 depending on the application requirements. The extraction phase 4 could be a polymeric layer prepared on the wire surface, particulate adsorptive or absorptive material glued or otherwise affixed to the wire surface, or immobilized biorecognition agents such as antibodies nucleotides or protein receptors. When constructed of the stainless steel wire described below the extraction device is quite flexible. It will follow curves in a vein or catheter and normally resume a straight configuration when removed. The device is useful for the application of monitoring concentrations of drugs and their metabolites in blood or other tissues, either in single point monitoring or in multiple point (time course) monitoring.
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> Figure 1, part B illustrates standard medical catheter is shown in schematic form having a catheter body 10 and a sealing septum 12 (PRN). PRN is the commonly used term for an i.v. adapter to seal a catheter, incorporating a piercable septum, marketed by Beckton Dickinson. In the text that follows applications are described that use such a catheter for intra venous (i.v.) sampling. In practice, catheters are available for accessing other vessels as well, so applications are not limited to i.v. ones. For instance arteries,

> vessels within organs or capillaries may also be accessed using similar devices.

3.2. Amendments to Claim 102

Having regard to Claim 102, the amendment stating that the coated end of the fibre is further coated with a polymeric bioprotection layer is supported by the previous wording of the claims, as well as by the application as filed, for example at description page 19 (line 30) to page 20 (line 4), which refers to the "inner coating" or extraction phase, as well as the "outer coating" or biocompatible layer that protects against absorption of proteins:

> Figure 8 shows the catheter with the hollow fibre 38 coated on the inside wall surface at the lower portion 70 of the fibre. The schematic cross sectional view shows the two layer coating 66 ad 64 on the inner fibre surface 62. The outer coating 66 is chosen to be biocompatible to eliminate absorption of proteins, while the inner coating 64 is the extraction phase facilitating removal of well defined components from sample introduced to the inner fibre via channel 68.

Also, at page 22 (lines 15 to 20) use of an outer biocompatible layer is described:

> Improved biocompatibility in the extraction phase would be beneficial to extend either the time period the phase can be in contact with tissues, or increase the number of samplings that can be made from one site. This can be achieved in two different ways. Either new phase with better biocompatibility could be selected or a biocompatible outer layer could be used in conjunction with an inner extraction phase having lower biocompatibility.

Further, in the passage at page 22 (lines 24 to 27) it is emphasized that it is the extraction phase itself that is coated with the biocompatible protection layer:

> If it is desirable to use a less biocompatible extraction phase the device could be rendered biocompatible by ***coating the extraction phase*** with an outer biocompatible layer such as derivatized cellulose.(emphasis added)

3.3. Amendments to Claim 105

The amendment made to claim 105, indicating that the extraction phase is loaded with calibrant prior to sampling, is clearly supported by the application as filed, for example in the passage found on page 9 at lines 6 to 8:

> In one embodiment of the invention, the extraction phase may additionally comprise a strongly bound calibrant which is retained in the extraction phase during the step of adsorbing.

Additionally, at page 15, lines 3 to 5, pre-loading of the extraction phase is discussed:

> Under non-equilibrium extraction or where it is not possible to match in vitro samples to the in vivo system, calibration may be achieved by pre-loading the fibre with a suitable calibrant.

Further, at page 25, lines 25 to 27, pre-loading of the extraction phase is again discussed:

> As an alternative to conventional internal standard calibration, a standard may be loaded onto the fibre (extraction phase) prior to analysis and the loss of standard from the fibre is monitored instrumentally.

Considering each of the passages of support provided above, it should be clear that each amendment finds support in the specification, drawings, and claims as originally filed.

4. Claim Rejections under 35 USC 103

Claim 101 was primarily rejected due to the teachings of Pompidou et al., and Gourley et al. In the interview with the Examiner, agreement on amendments to distinguish over Pompidou et al. was reached. All other claims depend from claim 101, and thus it is believed that by traversing the objections raised to claim 101, other objections raised to dependent claims need not be addressed.

Objections raised to previous claims 102, 103 and 105 under 35 USC §103 will be addressed briefly here, as amendments made to claims 102 and 105 serve to further distinguish over the cited references.

4.1. Objection Raised to Claim 101

The reference of Pompidou et al. shows in Figure 1, a flexible rod, having a support around the full length of which is wound a “ribbon”. This ribbon is not limited to the end portion of the rod or support, but extends upward of the terminal end. Although the Examiner may consider the ribbon itself to be somewhat parallel to an extraction phase (because it contains antibodies on its surface), but it can now be clearly seen that it is not limited to the end of the rod of support, as is now specified in claim 101 (“consisting of a coated end”). By including this amendment to specify that the coating is limited to the end of the fibre, claim 101 now clearly distinguishes over the wound-up ribbon of Figure 1 of Pompidou et al.

In column 2 of Pompidou (lines 37 to 39), it is stated:

> The active layer surrounding the rigid support can be a flat ribbon or a round cord on which the reagents are deposited and fixed. It can involve ligands and, notably, antigens or antibodies, but also nucleotides. Thus, in this embodiment the microsystem consists of a support coming in the form of a ribbon wound around one end of the flexible rod. An example of this embodiment is represented on FIG. 1 of the attached drawings.

This emphasizes that the "active layer" is not intended to be restricted to a terminal end of the rod or support. There is no depiction or suggestion in Pompidou et al. that the "active layer" of a microsystem be limited to a terminal end. Further, combining the teachings of Pompidou et al. and Gourley et al. would not provide this missing element, as the "sensing element" of Gourley et al. includes a glass sleeve surrounding the sensing element, which renders the device inflexible. Flexibility is negated by the requirement for the glass sleeve in Gourley, and is clearly not required in claim 101 as amended.

The latter amendment to claim 101, that the fibre holding region is attached to the end of the fibre opposite to the coated end, is a further departure from the teachings of either Pompidou et al and Gourley et al. Specifically, Pompidou et al. provides no depiction whatsoever of the end of the support or rod that is opposite to the ribbon. In Figure 1 of Pompidou et al, the ribbon appears to wind all the way to the very top (or proximal end) of the rod or support, and is only implied to be present at the bottom (or distal end) of the rod or support, since the depiction appears to provide only a partial tear-away cross-section of the device. From this figure, it can only be implied that the ribbon winds up the entire length of the rod or support, in which case, there can be no "opposite end" defined at which a holding region is located.

In the descriptions of Figures 2 and 6 of Pompidou et al., showing bound antibodies with adsorbed entities, there is no suggestion that this region containing bound antibody be limited to one end, while the other end contain a holding region. A proximal end is not depicted or discussed in Pompidou et al., and thus, the document is completely silent on the presence of a holding region or equivalent, much less the placement of such a component.

Similarly, Gourley et al. provides no depiction of an end other than the distal terminal end of the device, at which can be found the sensing element and glass sleeve. There is no discussion of what may be present at the opposite (or proximal) end, or how an element

disposed at the proximal end may be used to move the device with respect to a catheter or blood vessel.

Thus, the amendments made to claim 101 provide further distinctions of the invention over the combined teachings of the applied references. It is therefore requested that the objection raised to claim 101 and to all subsequent claims depending therefrom be withdrawn.

4.2. Objection Raised to Claim 102 and 103

Claims 102 and 103 were rejected as being obvious in view of Pompidou et al. in combination with Gourley et al. The Examiner believes that overcoating taught by Gourley et al., is parallel to the polymeric biocompatible protection layer of claim 102. Note that claim 102 has been amended to more specifically indicate the location of the polymeric biocompatible protection layer as being coated end of the fibre (which is stipulated in claim 101 as coated with the extraction phase). This distinguishes further over Gourley et al., because the rigid sleeve of Gourley et al. surrounds the "sensing element". See Figure 1 of Gourley et al., for example, where overcoating (20) is shown as surrounding the glass sleeve (19). In the instant invention, no glass sleeve or rigid member is required, and the extraction phase itself (the coated end of the fibre) is directly coated with the protection layer. Pompidou et al. does not teach any such protection layer.

4.3. Objection Raised to Claim 105

In the rejection of claim 105, the Examiner has combined the teachings of three references: Pompidou et al, Gourley et al. and Riviere et al. Now that claim 105 has been amended to emphasize that the extraction phase is loaded with calibrant ***prior to*** sampling, the objection should be rendered moot. None of the cited references teaches that the calibrant be included within the extraction pha*se prior to sampling.* This is not the same as spiking a sample with a calibrant. Independent claim 105 specifies that the calibrant is contained within the extraction phase, not simply as a result of exposure to a sample containing calibrant, but as an intentional result of pre-loading. Calibration standards are assessed by Riviere et al. by dissolving each individual solute in water as a solvent. There is no suggestion that such a calibrant be added to the membrane of Riviere et al., for example, or to any coating surrounding a fibre.

As emphasized in the previous response, Riviere et al. may place the calibrant into the system under investigation (via "spiking" of the investigated system). In a biological system where the device is intended for placement into a blood vessel, this would be the equivalent of injecting a calibrant into the blood stream, which is *NOT* the same as placement of a calibrant into the extraction phase coated onto a fibre that is then placed into the blood stream. In the former instance, the calibrant would rapidly circulate around the bloodstream of the system under investigation, and would become dilute at the site of sampling and/or the site of injection. This dilution effect would render useless the meaning of the calibrant, unless the entire bloodstream of the animal under investigation was to be allowed to equilibrate with a constant level of calibrant. By way of contrast, the approach to calibration as recited in claim 105 is compatible with in-vivo monitoring since the calibrant itself primarily remains intact within the extraction phase, or allows only small amount of calibrant to possibly enter the blood stream or investigated tissue. This avoids the problem of contamination of the whole investigated system as in a typical "spiking" scenario.

The specific passages of Riviere et al. referred to by the Examiner at paragraphs 0167-0170 are not equivalent to the inclusion of a calibrant in the extraction phase as claimed in claim 105. The calibration compounds listed in these paragraphs are NOT coated onto fibers, are NOT included in any type of extraction phase, and are NOT exposed to a sample. These calibration standards are simply run concurrently with samples. The phrase "descriptor matrix" as used in [0167] clearly refers to the numerical matrix of *values* that each calibrant molecule can be found at, used for statistical purposes in the comparative matrix of calibrant samples that were run. The calibrant samples were run *separately* from analysis of actual sample coatings, and only for the purpose of ensuring accurate calibration. There is no passage in Riviere et al. indicating that any *extraction phase* or coating found on a fibre is altered to contain a calibrant.

Simply running concurrent samples containing calibrants would not lead a skilled person to include a calibrant in a coating or extraction phase. In fact, the opposite is true, as the use of calibrants by Riviere et al. simply reinforces conventional use of calibrants being evaluated as

"standards" in parallel with "samples". Including a calibrant within the extraction phase is a departure from this conventional mode of calibrant use.

It is requested that the Examiner reconsider the objection raised to the claims in view of the amendments now put forth and the above-noted arguments. Withdrawal of the obviousness objections on this basis is respectfully requested.

5. Conclusion

It is requested that the Examiner reconsider the objection raised to the claims in view of the above, and withdraw the obviousness objection on this basis.

The Applicant believes that no fee is due with this submission, but nevertheless authorizes the Commissioner to debit any required fee from or credit any overpayment to Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP.

It is submitted that this application is in condition for allowance. Early and favorable reconsideration is respectfully requested.

Respectfully submitted,

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